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A case of giant prolactinoma, initially misdiagnosed as sinonasal neuroendocrine carcinoma☆

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ABSTRACT

Giant prolactinomas are defined as pituitary tumors greater than 4 cm, often associated with very high prolactin level (>1000 ng/mL). They are relatively rare tumors and can present differently from typical prolactinomas. They can be highly invasive, resulting in acute neurological complication at the time of presentation. We present a case of a young woman with giant prolactinoma initially misdiagnosed as sinonasal neuroendocrine carcinoma. The acute presentation of headache, ptosis and impending brain herniation, requiring emergent ventriculostomy and intubation, led to the clinical suspicion of a more sinister diagnosis. Transnasal biopsy of the mass was consistent with sinonasal neuroendocrine carcinoma, and chemotherapy was planned. Laboratory testing, however, revealed an elevated prolactin (27,400 ng/mL, after 1:100 dilution). Re-review of pathology with additional immunohistochemical staining was requested and confirmed the diagnosis of prolactinoma. After 5 months of cabergoline treatment, prolactin level has decreased to 118 ng/mL. There has been a marked reduction in tumor size and an almost complete resolution of neurological symptoms. Given their atypical presentation and potential for sharing common immunohistochemical stains with other neuroendocrine neoplasms, giant prolactinomas extending into the nasal cavity can be misdiagnosed as other neuroendocrine neoplasms which may develop at this site. Accurate diagnosis is imperative to prevent unnecessary surgery and/or radiation and to ensure implementation of dopamine agonist therapy.

Introduction

Giant prolactinomas are generally defined as pituitary tumors greater than 4 cm in diameter with high baseline prolactin (PRL) levels (often above 1000 ng/mL) [1]. They are very rare, representing only 2%–3% of all PRL-secreting tumors [2]. They are most commonly found in young- to middle-aged men with a male-to-female ratio of about 9:1 [1,2]. Giant prolactinomas can be highly invasive resulting in neurologic complications [3]. On imaging they can present as aggressive skull base tumors and pathologically they have the potential for sharing common immunohistochemical (IHC) stains with other neuroendocrine neoplasms. Given their rarity and sometimes atypical presentation, diagnosis can be surprisingly delayed or even missed in some cases, having the potential to lead to unnecessary surgery and/or radiation. Correct diagnosis is paramount to ensuring appropriate dopamine agonist therapy.

Case report

A 27 year old female presented to the emergency room with progressively worsening headache associated with nausea, vomiting and 2–3 days of left eye ptosis. Her condition rapidly declined; she developed asymmetrical pupil dilation due to impending brain herniation, and required intubation. Initial head CT and MRI showed a large destructive mass centered at the central skull base, measuring 8.1 cm in craniocaudal dimension with extensive bony destruction, intracranial and intraorbital extension, and acute obstructive hydrocephalus, with differential diagnosis including destructive pituitary adenoma/carcinoma, sarcoma, atypical destructive lymphoma or primary sinus neoplasm (Fig. 1). An urgent ventriculostomy catheter was placed; she was started on high dose dexamethasone and admitted to the neurosurgical ICU. Patient underwent transnasal biopsy of the mass and initial pathology assessment reported moderately to poorly differentiated sinonasal neuroendocrine carcinoma (SNEC). IHC staining was strongly positive for CD56, synaptophysin and CAM5.2, focally positive for S-100 and pancytokeratin and negative for chromogranin. Prolactin staining was not performed. Positron emission tomography imaging was negative for metastatic disease. Given the pathology results, location of the tumor, and invasion to surrounding structures, neo-adjuvant

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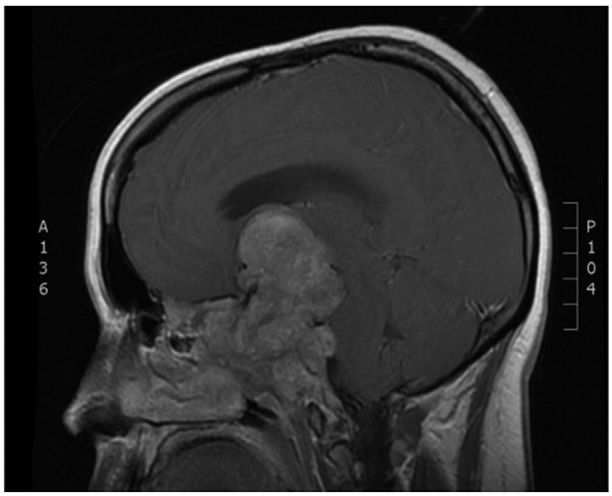

Fig. 1. Magnetic resonance image of head, T1-weighted sagittal post gadolinium, demonstrating large heterogeneous skull base tumor with intra cranial, intra-orbital and nasopharyngeal extension.

chemotherapy was recommended by the oncology service to attempt to shrink the mass, followed by re-staging scan with subsequent potential chemo-radiation for definitive treatment. Endocrinology was later consulted due to a significantly elevated prolactin level of >4700 ng/mL which was measured a few days after admission. Further history from the patient was pertinent for primary amenorrhea, galactorrhea and hirsutism. Review of her labs showed: serum prolactin 27,400 ng/mL (measured at 1:100 dilution) (Ref: 4.8–23.3 ng/mL), TSH 0.15 mIU/L (Ref: 0.47–4.68 mIU/L), FT4 0.7 ng/dL (Ref: 0.6–2.5 ng/dL), LH <0.2 mIU/mL, FSH <0.7 mIU/mL, estradiol 5.3 pg/mL(Ref: 12.5–211 pg/mL), IGF-1 171 ng/mL (Ref: 78–270 ng/mL). Hypothalamic–pituitary–adrenal (HPA) axis could not be assessed since patient was on glucocorticoids. In view of her history and laboratory findings, suspicion for a prolactin-producing adenoma was high. Re-review of pathology was requested resulting in an amended report which read, "after further clinicopathological correlation and additional IHC staining," this confirmed the diagnosis of "pituitary prolactin adenoma, acidophilic stem cell subtype"(Fig. 2). IHC staining was strongly positive for prolactin, CD56, synaptophysin, p53 and CAM5.2 and focally positive for S-100, Ki-67 and pancytokeratin. It was negative for TSH, LH, ACTH and chromogranin. There was scant positivity for GH. Chemotherapy was withheld, and she was started on cabergoline 0.5 mg twice weekly, later up-titrated to 1 mg 3 times per week and thyroid hormone replacement. Five months after the start of cabergoline her prolactin level is 118 ng/mL. Most recent MRI, five months post-start of cabergoline, revealed marked reduction in tumor size to less than 4 cm (Fig. 3). Clinically, she has had almost complete resolution of left eye ptosis and significant improvement in visual fields. Her HPA axis, assessed after discharge by ACTH stimulation test, was intact.

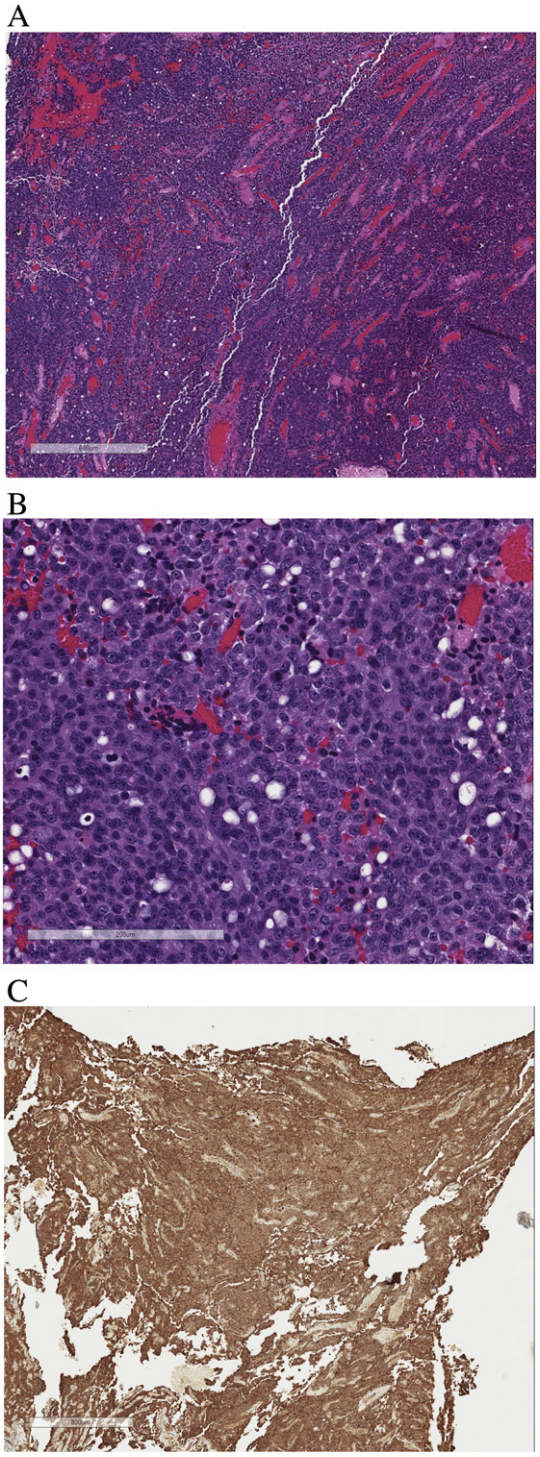

Fig. 2. A. Hematoxylin & eosin (H&E) stain, low magnification. B. Hematoxylin and eosin (H&E) stain, high magnification. Cells demonstrating pink cytoplasm which is typical for acidophilic cells. C. Prolactin stain.

Discussion

Giant prolactinomas can cause both diagnostic and therapeutic challenges given their rarity, atypical presentation and potential radiologic and pathologic overlap with other neuroendocrine neoplasms. Specific definition of "giant" pituitary adenomas was introduced in 1979 by Symon et al. for adenomas extending by more than 40 mm in any direction from the midpoint of the jugum sphenoidale. A tumor size criterion is universally recognized and is important as these tumors will cause specific neurological complications related to their invasive nature. The most commonly used criterion is by far a tumor diameter of 40 mm or more [1]. This particular size has been defined arbitrarily by similarity with the dimensions of the so-called giant cerebral aneurysms. As serum hormone levels generally parallel tumor size, giant prolactinomas are typically associated with very high PRL concentrations, above 1000 ng/mL [1,4]. Unlike typical pituitary prolactinomas which classically present with amenorrhea, infertility and galactorrhea in premenopausal women, giant prolactinomas can present with neurologic complications such as cranial nerve paresis, visual defects, hydrocephalus, exophthalmos or optic nerve compression due to massive extension into surrounding structures [5,6]. In very rare cases when there is a large tumoral extension into the nasopharynx, the diagnosis may be made through biopsy of a nasal mass [7], as we reported in this case. Interestingly, in

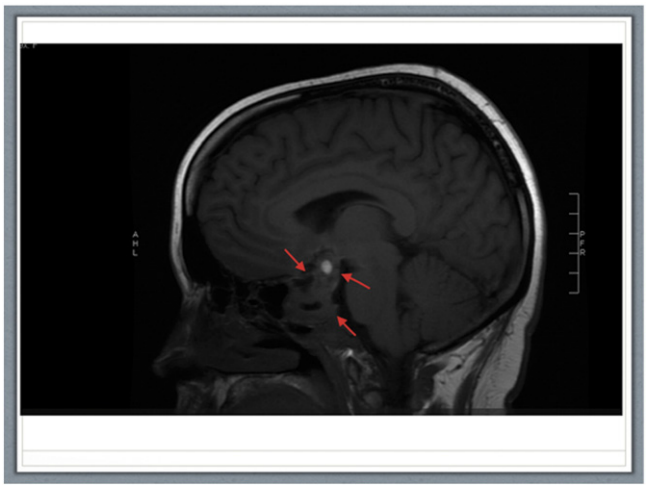

Fig. 3. Magnetic resonance image of head. T1-weighted sagittal view, demonstrating significant decrease in tumor size.

this case report by Care et al., the initial histological diagnosis was also a low grade neuroendocrine carcinoma, before diagnosis of prolactinoma was confirmed [7]. Therefore, although rare, giant prolactinoma should always be considered in the differential diagnosis of any large skull base tumor invading the nasopharynx. On the other hand, neuroendocrine carcinoma of paranasal sinuses is an exceedingly rare malignancy, accounting for 5% of tumors at this site [8]. They are known for their aggressive behavior and poor response to treatment. In a retrospective review of 28 patients with histological diagnosis of SNEC by Mitchell et al. [8], the most common site of tumor origin was ethmoid sinus followed by nasal cavity. Of note, in 10% of cases tumor originated from sphenoid sinus which could mimic pituitary adenoma or other sellar masses radiographically. Tumors of neuroendocrine differentiation show common ultrastructural and immunohistochemical features, including dense core secretory granules, staining for chromogranin, synaptophysin, and keratin. Since prolactinomas also express common neuroendocrine markers seen in other neoplasms with neuroendocrine differentiation, misdiagnosis as other neuroendocrine neoplasms is not unexpected; particularly when the diagnosis is made through biopsy of nasal mass rather than classical sellar mass. Correct diagnosis is particularly important, as dopamine agonists (DAs) are first-line treatment and can result in PRL normalization, marked reduction in tumor size and even improvement of acute neurologic complications in majority of cases [9]. In series with giant prolactinomas, resistance to cabergoline varies between 16% and 50% [9]. DA resistance has been defined as failure to normalize PRL on maximally tolerated doses of DAs and the absence of tumor size reduction ≥50%. Although most reported cases in the literature typically respond to DAs, a normal PRL level may not be achieved due to the large tumor size and very high PRL level at the time of diagnosis. True resistance to DAs (complete absence of response) is rare and may be indicative of malignancy. In another review of individual responses of 97 patients with giant prolactinoma to DA therapy, 60% (58/97) of patients achieved normoprolactinemia, 74% (65/88) had marked reduction in tumor size and 96% (28/29) had improvement in visual field. As we learned from this case, it is imperative that clinical history, laboratory and imaging findings be reviewed, corroborated and discussed with the pathologist so pertinent IHC can be performed to confirm the diagnosis.

Conclusion

Given their atypical presentation and potential for sharing common IHC stains with other neuroendocrine neoplasms, giant prolactinomas extending into the nasal cavity can be misdiagnosed as other neuroendocrine neoplasms which may develop at this site. This case highlights the importance of taking a detailed clinical history along with full pituitary hormonal evaluation in the assessment of large skull base tumors. Accurate diagnosis is paramount to prevent unnecessary chemotherapy, surgery and/or radiation and to ensure implementation of dopamine agonist therapy.

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